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REVIEW

Pheochromocytoma: A review on preoperative treatment with phenoxybenzamine or doxazosin

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ABSTRACT

Background: During surgical treatment of pheochromocytoma, haemodynamic instability may occur. To prevent this, patients receive preoperative treatment with an alpha-blocker. Nowadays, some centres use phenoxybenzamine, while others use doxazosin. The purpose of this review is to analyse the current evidence of the benefits and risks of phenoxybenzamine and doxazosin in the preoperative treatment of pheochromocytoma.

Methods: The literature was reviewed by searching PubMed using the following search terms: pheochromocytoma, phenoxybenzamine, doxazosin and alpha-blockade. The filter was set on English language.

Results: No randomised controlled trials were found. Five follow-up studies comparing phenoxybenzamine and doxazosin in the treatment of pheochromocytoma were retrieved and analysed. There was a trend that systolic arterial pressure is slightly better controlled by phenoxybenzamine. However, this resulted in more pronounced postoperative hypotension as well. The use of an alpha-blocker was often accompanied by other vasoactive agents. Phenoxybenzamine was often accompanied by a beta-blocker to control reflex tachycardia, while patients on doxazosin received significantly more additional antihypertensive medicines. Most of the studies showed that the use of vasoactive drugs and fluid infusion does not differ significantly between the two drugs. Phenoxybenzamine caused significantly more orthostatic hypotension, oedema and complaints of a stuffy nose.

Conclusion: On the basis of the current evidence, there is no evidently superior alpha-blocker for the pretreatment of patients with pheochromocytoma. Perioperative haemodynamics seem to be slightly better controlled with phenoxybenzamine, at the cost of more pronounced postoperative hypotension. Side effects occurred less often in the doxazosin group.

KEYWORDS

Pheochromocytoma, phenoxybenzamine, doxazosin, alpha-blockade

INTRODUCTION

Pheochromocytoma is a rare tumour originating from the catecholamine-producing chromaffin tissue in the adrenal medulla or the extra-adrenal paraganglia.[1] Incidence among the general population is about 0.8 per 100,000 person-years, and is estimated to be 0.1-0.6% in the hypertensive population.[2,3] Diagnosis usually takes place in patients aged 40-50 years.[4] However, hereditary variants, such as multiple endocrine neoplasia type 2, Von Hippel-Lindau disease, neurofibromatosis type 1 and the pheochromocytoma-paraganglioma syndrome, can present earlier.[5] A history of episodic tachycardia, sweating, headache and signs of paroxysmal hypertension is classic.[6,7] These symptoms arise as a consequence of excessive catecholamine release. Between episodes blood pressure can be normal. However, clinical presentation can differ, depending on the catecholamine-releasing profile of the tumour. A tumour predominantly secreting epinephrine is usually associated with paroxysmal hypertension, while the norepinephrine-secreting variant is associated with sustained hypertension.[8,9] Pheochromocytoma is diagnosed by biochemical testing: plasma or 24-hour urinary fractionated metanephrines, further imaging and pathological confirmation.[10] The imaging consists of an abdominal or pelvic CT scan, MRI or even 123I-MIBG scintigraphy and FDG-PET to determine the exact site of the tumour.[11,12] The only definitive treatment consists of surgical resection. During manipulation of the tumour, dangerous amounts of catecholamines can be released in the circulation,

resulting in life-threatening events, including hypertensive crises, cardiac arrhythmias, myocardial infarction or ischaemia, pulmonary oedema and multiorgan failure.[13-16] Furthermore, the rapid decrease of catecholamines after surgery may result in severe hypotension.[16,17]

To prevent these life-threatening events from happening, preoperative management has been recommended. One of these therapies is the use of alpha-adrenoceptor blockers, which can counter the adrenergic effects of catecholamines.[18] In addition, alpha-blockade permits intravascular volume expansion.[19] Nowadays, some centres use the non-selective alpha-blocker phenoxybenzamine, while others use the selective alpha-blocker doxazosin.[20] Although both compounds have been used for a long time and proved to result in reduction in operation mortality, neither of them is officially registered for the preoperative management of pheochromocytoma.[20-24]

PHARMACOLOGICAL PROPERTIES

Phenoxybenzamine is a non-competitive, long-acting, alpha-1- and alpha-2-adrenoceptor antagonist.[20,23,25] The usual starting dose is 10 mg twice daily per os and can be increased until control of blood pressure (<160/90 mmHg) or orthostatic hypotension arises.[3,18,20] The hypothetical advantage of the non-competitive action is that even when excessive amounts of catecholamines reach the circulation, alpha-blockade is still effective. A disadvantage is the high incidence of reflex tachycardia, due to the inhibition of the alpha-2 adrenoceptors localised in the presynaptic membrane. Stimulation of these presynaptic receptors inhibits norepinephrine release. Blockade results in a disturbance of the negative feedback loop and, as a consequence, an increase in chronotropic activity.[9,20] Therefore, a beta-blocker is often added to phenoxybenzamine therapy in order to decrease chronotropic activity. Moreover, phenoxybenzamine causes central sedation, headaches and is long acting, which may cause prolonged hypotension postoperatively.

Doxazosin is a competitive, short-acting, selective alpha-1-adrenoceptor antagonist.[20,24,25] These properties offer some possible advantages. Doxazosin does not cause reflex tachycardia and has a relatively short duration of action because of its competitive inhibition, possibly shortening the hypotensive period postoperatively. Although it is relatively short-acting, the plasma half-life is 22 hours; therefore it can be dosed once daily. The starting dose is usually 1 mg per os, with a recommended maximum of 16 mg a day. Furthermore, doxazosin does not cause central signs – unlike phenoxybenzamine it does poorly pass the blood-brain barrier – or peripheral oedema.[26] As a consequence of its competitive property, blockade may be ineffective during high plasma concentrations of catecholamines, for example occurring during tumour handling.

No consensus about the optimal regimen has been reached so far.[20] The purpose of this review is to analyse the current evidence of the benefits and risks of phenoxybenzamine and doxazosin in the preoperative management of pheochromocytoma, in order to find out whether there is an optimal regimen concerning intraoperative haemodynamics. Secondary outcomes are side effects and amount of fluid and vasoactive drug administration.

METHODS

The literature was reviewed by searching PubMed using the following search terms: pheochromocytoma, phenoxybenzamine, doxazosin and alpha-blockade. The filter was set on English language. No randomised controlled trials directly comparing the two compounds were found. Five follow-up studies comparing phenoxybenzamine and doxazosin in the treatment of pheochromocytoma were retrieved and analysed.

RESULTS

An overview of the retrieved studies is presented in *table 1*.

Prys-Roberts *et al.*

Prys-Roberts *et al.*[26] compared phenoxybenzamine versus doxazosin in the preoperative treatment of pheochromocytoma. Thirty-five patients diagnosed with pheochromocytoma or paraganglioma were included in this prospective follow-up study. Between 1990 and 1992, eight patients were included for the phenoxybenzamine group, receiving 20-120 mg per day. Doses were increased until orthostatic hypotension occurred or the patient complained of a stuffy nose. All eight patients received additional beta-receptor blockade therapy with propranolol (n=4), metoprolol (n=2), labetalol (n=1) or atenolol (n=1). Between 1993 and 2001, 27 patients received doxazosin 2-16 mg per day, the maximum dose depending on the blood pressure and mild orthostatic hypotension. The first four patients and five out of the subsequent 23 patients received additional beta-receptor blockade. These five patients had tachycardia as a result of an epinephrine-secreting tumour. Heart rate (HR), systolic (SAP) and diastolic arterial pressure (DAP) were continuously measured perioperatively. The amount of vasoactive drugs used and side effects were monitored as well.

Table 1. *Overview of the retrieved studies*

Reference	Study type	Number of patients	Intervention		Outcome				Bias
			Phenoxybenzamine	Doxazosin		PXB	DOX	Significance (P<0.05)	
Prys-Roberts, 2002	Prospective follow-up study	PXB n=8 DOX n=27 Patients diagnosed with pheochromocytoma or paraganglioma (n=3)	Daily dose 20-120 mg (in three times daily) β-blocker (n=8, (100%))	Daily dose 2-16 mg β-blocker (n=9, (24%))	Preoperative SAP (mmHg) DAP (mmHg) HR (beats/min) During anaesthesia SAP (mmHg) DAP (mmHg) HR (beats/min) Peak during tumour handling SAP (mmHg) DAP (mmHg) HR (beats/min) Postoperative SAP (mmHg) DAP (mmHg) HR (beats/min) Vasoactive drugs Phentolamine (mg) Labetalol (mg) Side effects Orthostatic hypotension (%) Oedema (%) Fluid retention (ml) Stuffy nose (%)	 162±17.7 92±15.3 71±12.6 98±5.9 59±7.6 51±3.7 185±32.5 102±14.4 94±9.7 100±11.9 55±7.1 61±6.9 96±6.8 33.1±8.4 n= 8 (100) n= 7 (88) 4794±2474 n= 8 (100)	 148±21.1 78±13.6 72±11.5 97±6.9 52±6.5 59±5.0 178±29.9 95±17.3 78±13.9 116±14.8 64±8.5 71±10.1 11.1±7.6 15.8±8.2 n= 2 (7.4) n= 1 (4) 2828±1386 n= 0	 ns 0.029 ns ns 0.049 0.003 ns ns 0.013 0.004 0.007 0.010 ns ns 0.025	No randomisation, small sample size. Patients in PXB group were selected between 1990 and 1992, whereas DOX patients were treated from 1993 until 2001 The last 9 patients in the DOX group underwent laparoscopic surgery No correction for tumour size or excretion profile
Kocak, 2002	Retrospective follow-up study	PXB n=21 DOX n=17 (Prazosin n=11) Patients diagnosed with pheochromocytoma or paraganglioma (n=3)	Mean daily dose 105.7 mg (range 40-120 mg)	Mean daily dose 11.8 mg (range 4-32 mg)	Time for preparation (weeks) Preoperative blood pressure No. of patients with hypertension during surgery Hypertensive attacks during tumour manipulation (SAP>180 mmHg)	3.7 (R 2-6) No data 17 (81%) ~80%	4.1 (R 2-6) No data 14 (82%) ~80%	ns ns ns ns	No randomisation, small sample size. Different periods of inclusion, no patient selection The last 6 patients in DOX group underwent laparoscopic surgery. Absence of baseline table

					No. of patients with postoperative hypotension (SAP <100 mmHg)	6 (28%)	5 (29%)	ns
					Mean intraoperative fluid replacement (ml)	4328 (R 1700-6450)	4504 (R 2250-7000)	ns
					Mean postoperative fluid replacement (ml)	4697 (R 2100-6000)	3853 (R 1800-6000)	ns
Yu Zhu, 2010	Retrospective follow-up study	PXB n=31 DOX n=36 Unilateral pheochromocytoma largest diameter <6 cm No severe injury in the heart, lung or kidney	Daily dose 20-60 mg (two or three times daily) β-blocker (n=24, (77%)) Additional antihypertensive therapy (n=5, (16%))	Daily dose 4-16 mg (one to three times daily) β-blocker (n=4, (11%)) Additional antihypertensive therapy (n=14, (39%))	Preoperative SAP (mmHg) DAP (mmHg)	125±13.2 78±11.5	123±15.9 77±8.7	ns ns
					Haematocrit Before therapy After therapy	0.41 ± 0.039 0.37 ± 0.040	0.39 ± 0.045 0.36 ± 0.044	ns ns
					Before anaesthesia SAP (mmHg) DAP (mmHg)	132±20.6 82±12.3	145±16.3 86±13.1	<0.01 ns
					During anaesthesia SAP (mmHg) DAP (mmHg)	91±16.2 65±15.1	110±15.6 70±14.0	<0.01 ns
					During tumour handling SAP (mmHg) DAP (mmHg)	162±19.2 100±15.1	169±24.7 98±13.4	ns ns
					Removal of tumour SAP (mmHg) DAP (mmHg)	74±8.8 52±7.5	96±10.8 53±6.3	<0.01 ns
					Postoperative SAP (mmHg) DAP (mmHg)	111±13.1 71±10.0	112±14.1 72±9.2	ns ns
					Δ Blood pressure SAP (mmHg) DAP (mmHg)	88±10.4 48±12.2	73±15.7 47±11.7	<0.01 ns
					Preoperative period (days)	25±3.2	11±3.6	<0.001
					Estimated blood loss (ml) Blood transfusion (ml) Crystal solution infusion (ml) Colloidal solution infusion (ml)	270±181 282±56 2549±279 2100±247	260±188 252±51 2580±260 2083±254	ns ns ns ns

Table 1. *Overview of the retrieved studies*

Reference	Study type	Number of patients	Intervention		Outcome				Bias
			Phenoxybenzamine	Doxazosin		PXB	DOX	Significance (P<0.05)	
Weingarten, 2010	Retrospective follow-up study	PXB n=50 Alpha 1 group n=37	Mayo Clinic Phenoxybenzamine (n=49, (98%)) Daily dose unknown β-blocker (n=39, (78%)) Calcium channel blocker (n=11, (22%)) Metyrosine (n=3, (6%)) Oral sodium chloride (n=30, (60%)) Hydration iv (n=4, (8%))	Cleveland Clinic Selective alpha 1 antagonist (n=24, (65%)) Daily dose 2-10 mg Phenoxybenzamine (n= 6, (16%)) 7 patients received no treatment with alpha-blockade β-blocker (n=17, (46%)) Calcium channel blocker (n=11, (30%)) Oral sodium chloride (n=33, (89%))	Preoperative SAP (mmHg) Mean (mmHg) DAP (mmHg) Intraoperative peak SAP (mmHg) Mean (mmHg) DAP (mmHg) SAP ≥30% baseline (min) SAP ≥200mmHg (min) Lowest intraoperative SAP (mmHg) Mean (mmHg) DAP (mmHg) SAP ≤30% baseline (min) SAP ≤30% baseline (% anaesthesia time) Greatest HR (beats/min) HR ≥100 beats/min (min) Lowest HR (beats/min) HR ≤50 beats/min (min) Estimated blood loss (ml) Intraoperative crystalloid (L) Intraoperative colloid (L) Vasoactive drugs Nitroprusside (%) Nitroglycerin (%) β-blocker (%) Labetalol (%) Phenylephrine (%)	 139±22 99±18 83±12 187±30 136±20 109±18 2 (IQ 0-11) 0 (IQ 0-2) 73±14 55±11 46±9 28 (IQ 6-62) 15.7 (IQ 3.3-24.9) 104±28 0 (IQ 0-1) 47±10 2 (IQ 0-11) 75 (IQ 25-250) 3.0 (IQ 2.0-3.1) 0 62.0 2.0 52.0 24.0 56.0	 139±22 93±19 73±17 209±44 151±30 114±26 5 (IQ 0-22) 0 (IQ 0-7) 78±15 56±10 43±9 13 (IQ 3-49) 5.1 (IQ 0.9-16.0) 105±18 0 (IQ 0-1) 51±10 0 (IQ 0-7) 100 (IQ 82-250) 5.0 (IQ 3.4-6.4) 1.00 (IQ 0.5-1.0) 67.6 46.0 27.0 40.5 27.0	 ns ns ns 0.011 0.004 ns ns ns ns ns ns ns 0.026 ns ns ns ns 0.010 <0.001 <0.001 <0.001 ns <0.001 0.027 ns 0.009	No randomisation, small sample size. Surgery during different periods and in different clinics. BMI in Cleveland Clinic patients was significantly greater. Amount of catecholamines measured in plasma is unknown Not all patients with selective alpha-1 blockade received doxazosin

Bruynzeel, 2010	Retrospective follow-up study	PXB n=31 DOX n=42 Patients diagnosed with pheochromocytoma or paraganglioma (10%)	Daily dose 60 mg (20-210 mg) Propranolol (n=25, (81%)) NaCl 0.9%, 2l/day	Daily dose 24mg (8-56 mg) Propranolol (n=37, (88%)) NaCl 0.9%, 2l/day	At presentation SAP (mmHg) Mean (mmHg) DAP (mmHg)	140 (R 90-230) 100 (R 70-178) 80 (R 55-152)	150 (R 105-240) 108 (R 80-180) 90 (R 64-150)	ns <0.05 <0.05	No randomisation, small sample size. Patients in PXB group were selected between 1995 and 2003, whereas DOX patients were treated from 2003 until 2007 No correction for tumour size. Plasma norepinephrine is significantly greater in DOX group; no correction
					After α-blockade SAP (mmHg) Mean (mmHg) DAP (mmHg)	130 (R 97-183) 98 (R 67-137) 80 (R 48-113)	129 (R 95-178) 95 (R 70-127) 76 (R 55-105)	ns ns ns	
					Postoperatively SAP (mmHg) Mean (mmHg) DAP (mmHg)	125 (R 90- 180) 90 (R 60- 133) 72 (R 45- 110)	120 (R 71- 170) 81 (R 64- 127) 61 (R 40- 106)	ns <0.01 ns	
					Fluctuations MAP <60 mmHg (min) SAP >160mmHg Episodes Minutes	5 (R 0- 150) 1 (R 0- 9) 3 (R 0- 165)	10 (R 0- 85) 1 (R 0- 4) 13 (R 0- 70)	ns ns ns	
					Fluid administration	No data	No data	ns	
					Vasoactive drugs Esmolol (mg) Phenylephrine Nitroglycerine Norepinephrine Phentolamine	314-5 No data No data No data No data	95 No data No data No data No data	<0.05 ns ns ns ns	

PXB = phenoxybenzamine; DOX = doxazosin; SAP = systolic blood pressure; DAP = diastolic blood pressure; HR =; heart rate; NS =; not significant; IQ = interquartile range; R = range.

Preoperatively SAP and HR did not differ significantly between the phenoxybenzamine and the doxazosin groups. In the doxazosin group DAP was significantly lower. During anaesthesia all values were significantly lower than preoperatively. HR was significantly lower in the phenoxybenzamine group (51 vs. 59 beats/min, p=0.003), while DAP remained higher (59 vs. 52 mmHg, p=0.049). During tumour handling, blood pressure and HR rose significantly, but only HR was significantly higher in the phenoxybenzamine group (94±9.7 vs. 78±13.9, p =0.013). Postoperatively SAP, DAP and HR were significantly lower in the phenoxybenzamine group. Moreover, the alpha-blockade by phenoxybenzamine persisted significantly longer. There were no significant differences in the administration of phentolamine or labetalol during surgery. All patients in the phenoxybenzamine group complained of orthostatic hypotension and dizziness on standing, in contrast to 7% (n=2) in the doxazosin group, who had mild orthostatic hypotension. Oedema due to colloid infusion occurred more often in the phenoxybenzamine group (88% vs. 4%) and fluid retention was significantly higher (p=0.025).

Limitations of this study are non-randomisation and small sample size. Furthermore, the therapy between the groups was not similar: the phenoxybenzamine patients received significantly more beta-blockers and the last nine patients in the doxazosin group underwent laparoscopic surgery. Tumour handling might be different during laparoscopic surgery. Moreover, the operations in the phenoxybenzamine group took place during the early 1990s, while the doxazosin group were treated until 2001. Although they used the same lateral extraperitoneal approach, one can expect better equipment and surgery conditions during the last operations. Tumour size was not analysed in this study. Therefore, it is uncertain whether tumour size in the two groups is comparable. If not, tumour manipulation would be more difficult and catecholamine secretion might be greater, resulting in more unstable haemodynamics. Because of the different diagnostics in the first five patients in the phenoxybenzamine group, there is no catecholamine excretion profile or plasma concentrations of catecholamines. Even so, the authors did not correct for differences in profile. Particularly the latter can influence the intraoperative haemodynamics.

Kocak *et al.*

Kocak *et al.*[27] retrospectively analysed the preoperative preparation of 49 patients treated for pheochromocytoma (n=46) or paraganglioma (n=3) between 1985 and 2000. Non-selective alpha-blockade with phenoxybenzamine was given before 1994 in 21 cases. The mean final daily dose was 105.7 mg (range 40-120 mg). Selective alpha-blockade was given in the form of prazosin (n=11) between 1994 and 1997 and doxazosin (n=17) between 1997 and 2002. Mean daily doses were 14.2 mg (4-28 mg) and 11.8 mg (4-32 mg), respectively. All patients were dosed until they had no hypertensive episodes and blood pressure was lower than 150/90 mmHg for one week. None of the patients received additional beta-blockade. All patients underwent laparotomy, except for six patients in the doxazosin group; they underwent laparoscopic adrenalectomy. Outcomes were the time elapsed for preparation with alpha-blockade and the perioperative records of blood pressure, volume replacement and supplemental adrenergic agents.

Time elapsed for preparation varied between 2 to 6 weeks and did not differ significantly between groups (p>0.05). At induction of anaesthesia, none of the patients had hypertension. Hypertension during surgery did not differ significantly between groups. It occurred in 81% (n=17) of patients in the phenoxybenzamine group, 73% (n=8) in the prazosin group and 82% (n=14) in the doxazosin group. During tumour manipulation hypertensive crises were measured in approximately 80% of patients in all three groups. Hypertensive crisis was defined as a SAP >180 mmHg and/or the need for sodium nitroprusside infusion. Postoperative hypotension was defined as a SAP <100 mmHg. This occurred in 28% (n=6), 27% (n=3) and 29% (n=5) in the phenoxybenzamine, prazosin and doxazosin groups, respectively and did not differ significantly (p>0.05). The use of inotropic agents was not required. Crystalloid fluid infusion both intraoperatively and postoperatively did not differ significantly between all three groups (p>0.05).

A strong point of this study is the monotherapy given to each patient; comparison between the two alpha-blockers is therefore more reliable. Limitations are the small sample size and non-randomisation. Furthermore, baseline characteristics are not given; it is uncertain whether the groups are comparable. The phenoxybenzamine group were treated during an entirely different period and the last six patients in the doxazosin group were treated by laparoscopy. The potential differences in outcome are therefore not the sole effect of the alpha-blockers. Moreover, values of blood pressure are not given; the quantitative effect of alpha-blockade on blood pressure cannot be compared with the other studies in this review. This could be the result of a retrospective study where data were retrieved going back to 1985.

Yu Zhu *et al.*

This retrospective follow-up study[16] compared the effects of phenoxybenzamine versus doxazosin in the preoperative treatment of pheochromocytoma. Originally there were 142 patients with pheochromocytoma, of whom 67 were included. Inclusion criteria were: 1) symptomatic pheochromocytoma, 2) diagnosis confirmed both biochemically and by MRI or CT, 3) unilateral adrenal

gland localisation, 4) largest diameter of tumours <6 cm, 5) without concomitant hypertensive encephalopathy or injury to heart, lung or kidney, 6) operation through retroperitoneal 11th intercostal incision. Between 2003 and 2005, 31 patients were pretreated with phenoxybenzamine, while 36 patients treated between December 2005 and 2008 received a preoperative treatment with doxazosin. Phenoxybenzamine was dosed between 20-60 mg in two or three gifts daily. Doxazosin was given at between 4-16 mg a day; in both groups doses were adjusted according to blood pressure. Beta-blockers were added when tachycardia occurred, this happened in 77% (n=24) of cases in the phenoxybenzamine and 11% (n=4) of cases in the doxazosin group. Only three cases from the phenoxybenzamine group had a predominantly epinephrine-secreting tumour, whereas all four patients receiving beta-blocker in the doxazosin group had one. Additional antihypertensive drugs were added when the blood pressure remained >160/100 mmHg (phenoxybenzamine 16% (n=5) vs. doxazosin 39% (n=14)). The main outcomes were perioperative haemodynamics. An intra-arterial catheter was used to continuously measure the perioperative blood pressure. Secondary outcomes were haematocrit, time till optimal preoperative condition, estimated blood loss and fluid infusion.

During the entire treatment DAP did not differ significantly between the two groups, baseline SAP was similar in both groups. However, the SAP before anaesthesia, during anaesthesia and after tumour removal was significantly lower in the phenoxybenzamine group. Postoperatively, there was no significant difference in blood pressure. The fluctuations in SAP, measured during surgery, were significantly greater in the phenoxybenzamine group: 88±10.4 mmHg versus 73±15.7 mmHg (p<0.01), but there were no significant differences in peak SAP. The difference in fluctuation between groups is caused by the higher SAP directly after tumour removal in the doxazosin group, suggesting the intraoperative haemodynamics were more stable. The time till achievement of optimal preoperative condition was longer in the phenoxybenzamine group; 25 days versus 11 days (p<0.001). Haematocrit did not differ significantly between the groups. However, there was a significant decrease after drug therapy in both groups (phenoxybenzamine 0.41± 0.039 before treatment vs. 0.37±0.040 after treatment, doxazosin 0.39± 0.045 before treatment vs. 0.36±0.044 after treatment, p<0.05). Concerning the estimated blood loss and fluid infusion, there were no significant differences between the two groups.

Limitations of this study include non-randomisation and being completely unmasked. Furthermore, the sole effect of phenoxybenzamine and doxazosin was not analysed; there were significant differences in the use of beta-blockers and other antihypertensive agents. However, one could state that this does follow clinical practice. Moreover, because of more recent surgery in the doxazosin group results might be influenced. There was no correction for tumour excretion profile.

Weingarten *et al*.

In this retrospective study[28] patients were selected after laparoscopic treatment for pheochromocytoma in the Mayo or Cleveland Clinic. During 2003-2006, 50 consecutive patients from the Mayo Clinic were treated preoperatively for pheochromocytoma; their records were analysed. The records of 37 consecutive patients treated between 2005 and 2009 in the Cleveland Clinic were reviewed as well. In the Mayo Clinic 49 (98%) patients were treated with phenoxybenzamine till orthostatic hypotension was achieved, 39 (78%) patients received an additional beta-blocker and 11 (22%) received a calcium channel blocker. Three (6%) patients received metyrosine, a catecholamine synthesis inhibitor. Furthermore, 30 (60%) patients received oral sodium chloride and four intravenous hydration. In Cleveland Clinic, there was no predominant treatment regimen: 65% (n=24) of patients received selective alpha-blockade (2-10 mg per day) and 16% (n=6) phenoxybenzamine, seven patients did not receive preoperative treatment with alpha-blockade. In 46% of cases a beta-blocker was added, as were calcium channel blockers in 30% of cases. Oral sodium chloride was given to 33 patients (89%). Primary outcome was the perioperative haemodynamics. Fluid administration, estimated blood loss and vasoactive drugs were secondary outcomes.

Preoperative blood pressure values were comparable between groups. The maximum intraoperative values of SAP and MAP were significantly lower in the phenoxybenzamine group of the Mayo Clinic. However, Mayo Clinic patients spent a relatively longer time in a hypotensive state during surgery (≤30% baseline SAP/ anaesthesia time). Estimated blood loss was lower in the Mayo Clinic: 75 ml (25-150) versus 100 ml (82-250), as was fluid infusion. The use of the vasopressor phenylephrine during surgery was significantly greater in the Mayo Clinic: 56% (n=28) versus 27% (n=10).

Limitations are the non-randomisation and retrospective nature of the study. Moreover, the treatment regimens were highly variable, especially the ones in the Cleveland Clinic. Furthermore, not every patient received doxazosin, some received prazosin. The use of additional antihypertensive therapy and vasoactive agents during surgery differed considerably as well. There is no explanation why different time periods were chosen to compare groups. Furthermore, the body mass index in the Cleveland group was significantly greater (29.8±7.1 vs. 26.5±4.6, p=0.009). For these reasons it is difficult to extract a reasonable conclusion out of these data.

Bruynzeel *et al.*

Bruynzeel *et al.*[29] compared the effectiveness of phenoxybenzamine versus doxazosin in the pretreatment of pheochromocytoma or paraganglioma (10%). In this retrospective follow-up study 73 patients were included. Between 1995 and 2003, 31 patients received phenoxybenzamine (median 60 mg per day, range 20-270 mg) and in 25 cases (81%) propranolol was added. Whereas between 2003 and 2007, 42 patients were pretreated with doxazosin (median 24 mg per day, range 8-56 mg) and propranolol (88%, (n=37)). All patients received preoperative volume expansion by infusion of NaCl 0.9% 2 litres a day, for two days. Laparoscopic surgery was performed in 39% (n=12) of the phenoxybenzamine group and 52% (n=22) of the doxazosin group on the following conditions: tumour size was ≤6 cm and no suspicion of malignancy. Outcomes were the perioperative blood pressure, use of vasoactive drugs and amount of fluids administered during surgery. Secondarily they analysed the influence of an additional beta-blocker on haemodynamics as well.

Blood pressure at presentation – before the start of doxazosin treatment – was higher in the doxazosin group. However, after alpha-blockade blood pressures were comparable. There were no significant differences in blood pressure fluctuations between groups. Furthermore, MAP postoperatively in the phenoxybenzamine group was significantly higher. Concerning the vasoactive drugs, only esmolol was administered significantly more in the phenoxybenzamine group. Use of phenylephrine, nitroglycerin and phentolamine was comparable, as was fluid infusion. There was no significant difference in intraoperative or postoperative blood pressure instability when comparing therapy with or without an additional beta-blocker.

Limitations of this study were non-randomisation, retrospective study design and the different periods during which the two groups were treated. Furthermore, it is not clear whether the results were corrected for tumour size or excretion profile. Plasma norepinephrine was significantly higher in the doxazosin group. This might explain the higher blood pressure at presentation and the lower blood pressure postoperatively; a higher dose of alpha-blockade was required, consequently leading to a more pronounced decrease in blood pressure postoperatively.

DISCUSSION

On the basis of the five studies analysed in this review, one can state that both phenoxybenzamine and doxazosin are capable of perioperative blood pressure control in patients with pheochromocytoma. There seems to be a trend, although not reaching statistical significance in some studies, that SAP is slightly better controlled by phenoxybenzamine. However, this seems to result in more pronounced postoperative hypotension as well. Monotherapy is rarely an adequate management. Phenoxybenzamine often has to be accompanied by a beta-blocker to control reflex tachycardia, while patients receiving doxazosin received significantly more additional antihypertensive medicines, such as calcium channel blockers or ACE-inhibitors, to control blood pressure. The use of vasoactive drugs and fluid infusion does not differ significantly among most studies. Only Prys-Roberts reviewed the side effects of both alpha-blockers. Phenoxybenzamine caused significantly more orthostatic hypotension, oedema and complaints of a stuffy nose.

Most results of the analysed studies were consistent. SAP during anaesthesia and surgery did not differ significantly between groups, only Yu Zhu – during anaesthesia – and Weingarten – during surgery – found a significantly greater SAP in the doxazosin group. This could be an effect caused by the phenoxybenzamine itself, but the treatment regimens between the two groups in the study by Weingarten have many irregularities. It is therefore difficult to attribute this difference to the influence of phenoxybenzamine alone.

Prys-Roberts found that postoperative blood pressure was significantly lower in the phenoxybenzamine group and Weingarten stated that patients in the phenoxybenzamine group spent relatively more time in a hypotensive state. The postoperative blood pressures did not differ significantly in the studies by Kocak and Yu Zhu. Although the postoperative SAP was similar in Yu Zhu's study, it was significantly higher in the doxazosin group directly after tumour removal. In contrast, the results of Bruynzeel *et al.* show a significantly higher MAP in the phenoxybenzamine group postoperatively. This might be the result of significantly higher plasma norepinephrine levels in the doxazosin group, resulting in higher alpha-blockade doses and a greater decrease of plasma catecholamines after surgery.

As a result of comparable SAP before and during surgery, and lower blood pressure postoperatively, one can hypothesise that fluctuation of blood pressure intraoperatively is greater in the phenoxybenzamine group. This was analysed in the study by Yu Zhu, confirming this hypothesis. Bruynzeel *et al.* found no significant difference in blood pressure fluctuation, possibly as a consequence of the different tumour excretion profiles, rendering the postoperative MAP in the doxazosin group rather low. Although this slightly more pronounced decrease in blood pressure in the phenoxybenzamine group is something to be aware of, it has not been reported by the analysed studies as being clinically relevant.

The use of vasoactive drugs did not differ significantly in three out of the five studies. The difference in the study by Weingarten is explained by other first choice intraoperative vasoactive agents between hospitals. They did, however, use the vasopressor phenylephrine significantly more in the phenoxybenzamine group, possibly to compensate for the more pronounced perioperative hypotension. Bruynzeel *et al*. found a significantly greater use of esmolol in the phenoxybenzamine group, possibly the result of more frequent episodes of tachycardia related to the use of phenoxybenzamine.

Another mode of action of alpha-blockade is preoperative volume expansion by vasodilatation. Yu Zhu measured the difference in haematocrit before and after treatment with both compounds and found that there was a significant decrease, but no significant difference in decrease of haematocrit between the groups. This suggests that the effects of the two compounds are similar concerning volume expansion. Fluid administration during surgery was similar in both groups in the studies by Kocak, Yu Zhu and Bruynzeel. Weingarten found a greater use of intraoperative crystolloids in the Cleveland or doxazosin group. This might be the consequence of more blood loss during surgery, instead of smaller preoperative volume expansion. Since the groups in Weingarten *et al*.'s study are very hard to compare, it may be safe to conclude that volume expansion and the use of intraoperative fluids is similar in both compounds.

Side effects were only analysed in the study by Prys-Roberts. Although both groups consisted of a small number of patients, the results seem to be evident. Patients in the phenoxybenzamine group had significantly more complaints about orthostatic hypotension, oedema and stuffy nose, as was expected, considering the phenoxybenzamine dose was increased until signs of orthostatic hypotension and stuffy nose occur. This does not, however, explain the oedema. One possibility could be a greater amount of fluid infusion postoperatively, because of the lower blood pressures.

Limitations of this review are the filter settings on English language, possibly missing relevant literature in other languages. However, they are mainly derived from the used studies themselves. Nevertheless, all retrieved articles were used.

None of the used studies were randomised controlled trials. Therefore comparison between the two groups can prove to be difficult, as will be discussed later. Second, patients, doctors and researchers were not blinded for the treatments and research question. However, due to the retrospective nature of four out of five of the studies and the objective continuous measurement of blood pressure, we regard the effects of an unmasked study on the primary outcomes as minimal. Some of the data had to be retrieved from 1985, possibly resulting in information or recall bias. This might be the case in the study by Kocak *et al*. where the baseline table and quantitative data of blood pressure perioperatively are absent. Third, sample sizes in the studies were small, most likely the result of the low incidence of pheochromocytoma. This was especially the case in the studies by Prys-Roberts and Kocak. The first study included only eight patients receiving preoperative treatment with phenoxybenzamine, while the second included 21 and 17 patients in the phenoxybenzamine and doxazosin groups, respectively. As a consequence, the power of these studies is rather low. The influence of a selection effect on the results is considered low, due to the absence of loss to follow-up. Four out of the five studies included all patients being prepared with alpha-blockade during a certain period. Only the study by Yu Zhu used inclusion criteria to select patients, excluding the patients most at risk for hypertensive crises, possibly to diminish the effect of outliers concerning the haemodynamics. Therefore these results could be used when treating an average patient with pheochromocytoma.

There are several confounding factors that were not corrected for. First of all, it is often not the sole effect of alpha-blockade that was measured, but the effect of additional antihypertensive treatment as well. Only the study by Kocak used monotherapy preoperatively. Other studies often combined phenoxybenzamine with a beta-blocker, possibly enhancing the blood pressure controlling effects of phenoxybenzamine. One can state, however, that phenoxybenzamine and a beta-blocker are often used together in daily clinical practice. It is therefore not illogical to measure the effect of both when both are considered necessary. Moreover, Bruynzeel found no difference in perioperative haemodynamics with or without an additional beta-blocker. Although use of vasoactive drugs and fluid infusion intraoperatively can be considered confounding factors, they can be seen as a measure of haemodynamic instability as well. Even so, in most studies they did not differ significantly.

Second, patients in the phenoxybenzamine group were treated years before the last patients in the doxazosin group. Because surgical techniques, anaesthesia and multidisciplinary collaboration have been improved over the years, we can assume that the most recently operated patients underwent surgery under better circumstances.[30] It is, however, difficult to translate these findings to a quantifiable effect on intraoperative haemodynamics. In Weingarten's study, patients were partially treated during the same period. Although treated in different hospitals, they still found similar results as the other studies, potentially diminishing the influence of surgery periods.

Third, the operative approach differed between studies. In the studies by Prys-Roberts and Kocak the last nine and six patients, respectively, were treated by laparoscopic surgery, whereas the rest were treated by open surgery. All patients in Yu Zhu's study were treated with conventional open surgery; in contrast, all operations in Weingarten's study were laparoscopic. Bruynzeel included patients whom underwent both types of surgery and concluded that there was no difference in intraoperative blood pressure fluctuations, as did Tiberio *et al.*[31] However, it has to be noted that laparoscopic surgery is performed on relatively small tumours with no suspicion of malignancy. In the case of studies only using laparoscopic surgery there could be selection bias, although not mentioned, because only laparoscopically operable tumours were included.
Fourth, there was no correction for tumour size or excretion profile. Although they share a linear relationship, tumour size and plasma catecholamine levels are both independent risk factors for intraoperative catecholamine release and thus haemodynamic instability.[29,32,33] Furthermore, the degree of norepinephrine production is associated with intraoperative hypertension.[13] Correction is, however, very difficult; using stratification on a small sample size diminishes the already low statistical power.

When considering the fact that effects might be influenced by study design, bias and sample size, it seems that the results represent some of the properties of the used compounds. The non-competitive block of phenoxybenzamine resulted in the seemingly better controlled systolic blood pressure, whereas the relatively short-acting doxazosin had a less pronounced postoperative hypotension, which could be hypothesised considering the pharmacological properties of both compounds. There does not seem to be any difference in the use of fluids and vasoactive drugs. Although analysed in a very small sample size, side effects occur significantly less often in the doxazosin group.
Currently there are no guidelines that prefer a certain type of alpha-blockade. On the basis of current evidence there is no reason to prefer either of the two compounds concerning haemodynamics, since clinically relevant differences are minimal. As the two drugs do not seem to differ much in effectiveness of haemodynamic control, more practical reasons can tip the balance in favour of one compound. For example, Kocak and Bruynzeel both switched from phenoxybenzamine to doxazosin, because they had trouble acquiring the phenoxybenzamine. Side effects seem to be more favourable in the doxazosin group as well. Moreover, in some cases it was possible to use only a single dose a day in the doxazosin group, instead of multiple doses of phenoxybenzamine.
On the basis of the current evidence, it is difficult to gain a solid conclusion about which drug is superior. To reach a definitive conclusion a randomised study is warranted. Investigators of the UMC Groningen, the Netherlands, are preparing such a randomised study. This is necessary for the fine tuning of current management and could solve this dilemma. However, whether using phenoxybenzamine or doxazosin, mortality is extremely low and severe complications as a consequence of excessive catecholamine release rarely occur. Patients who died did so because of metastasis or were more than 30 days post-surgery. Some people are even starting to doubt the use of preoperative alpha-blockade at all, claiming that intraoperative use of vasoactive agents is sufficient to control haemodynamics.[34] Shao *et al.* showed that 59 normotensive patients with a pheochromocytoma did not benefit from pretreatment with alpha-blockade (n=38) when compared with no pretreatment (n=21).[35] Haemodynamics in both groups were similar, but the use of vasoactive agents and fluids were significantly greater in the doxazosin group. Whether giving phenoxybenzamine, doxazosin or nothing, all three options should be analysed in further prospective studies.

CONCLUSION

The operative treatment of pheochromocytoma can be considered safe. On the basis of current evidence there is no evident superior alpha-blocker for the pretreatment of patients with pheochromocytoma. Perioperative haemodynamics seem to be slightly better controlled with phenoxybenzamine, at the cost of more pronounced postoperative hypotension. Side effects occurred less often in the doxazosin group. The use of vasoactive drugs and fluid administration do not differ significantly. More practical factors as availability and experience of the treating physician may tip the balance in favour of one of the two compounds. Randomised studies are required to solve this problem.

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